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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

WEHBE, ANNE MARIE SABRINA

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 12 11 2002

169

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.  
**09/225,904**

Applicant(s)  
**Sidransky**

Examiner  
**Anne Marie Wehbé**

Art Unit  
**1632**



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on Oct 7, 2002
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1, 7-9, 12-14, 18, 22-26, and 30-36 is/are pending in the application.
- 4a) Of the above, claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1, 7-9, 12-14, 18, 22-26, and 30-36 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claims \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some\* c) None of:

- Certified copies of the priority documents have been received.
- Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
- Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\*See the attached detailed Office action for a list of the certified copies not received.

- 14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

The translation of the foreign language provisional application has been received.

## Attachments:

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| 1. Notice of Extensions (PCT/ISA/210)                          | 4. Interview Summary (PCT/ISA/210)                 |
| 2. Notice of Draftsperson's Patent Drawing Review (PTO-948)    | 5. Notice of Informal Patent Application (PTO 152) |
| 3. Information Disclosure Statement(s) (PTO-1449) Paper No(s): | 6. Other:  |

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### DETAILED ACTION

Applicant's amendment received on 10/7/02 has been entered. Claims 15-17, 19-21, and 27-29 have been canceled. New claims 34-36 have been added. Claims 1, 7-9, 12-14, 18, 22-26, and 30-36 are pending in the instant application. An action on the merits follows.

The text of those sections of Title 35, US code, not included in this action can be found in previous office actions.

#### *Claim Rejections - 35 USC § 112*

The rejection of claims 1, 7-9, and 12-33 under 35 U.S.C. 112, first paragraph, for lack of enablement, is maintained over original, amended, and new claims 1, 7-9, 12-14, 18, 22-26, and 30-36. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the rejection for reasons discussed in detail below.

The applicant's amendments to the claims have **overcome** the following issues, the lack of enablement for 5'ALT polynucleotides other than 5' ALT /p16<sup>INK4A</sup>, which contains exons 2 and 3 of p16, and 5' ALT/p15<sup>INK4B</sup> which contains exon 2 of p15, and the lack of enablement for any

remain. The modification fails to provide an enabling disclosure for treating a cancer associated with overexpression

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5' ALT /p16<sup>INK4A</sup> expression by local administration at the site of a tumor any polynucleotide comprising SEQ ID NO:1 operatively linked to a polynucleotide comprising exons 2 and 3 of the p16 gene, or for treating a cancer associated with decreased 5' ALT/p15<sup>INK4B</sup> expression by local administration at the site of a tumor any polynucleotide comprising SEQ ID NO:1 operatively linked to a polynucleotide comprising exon 2 of the p15 gene.

The applicant argues that there is no objective basis for the office to question whether the disclosed 5' ALT /p16<sup>INK4A</sup> and 5' ALT/p15<sup>INK4B</sup> are or can be expressed in cells *in vivo*. The previous office action stated that applicant's evidence of record only serves to demonstrate the presence of 5' ALT /p16<sup>INK4A</sup> and 5' ALT/p15<sup>INK4B</sup> transcripts in cells and that the specification does not provide any evidence that a polypeptides translated from these transcripts share any of the same properties or functions as the wild type p16 or p15 polypeptides respectively. The specification provides no evidence that these transcripts actually produce protein *in vivo* or that the proteins produced has any particular biological activity. In addition, the specification fails to provide any evidence which correlates either the lack of 5' ALT /p16<sup>INK4A</sup> or 5' ALT/p15<sup>INK4B</sup> expression or the expression of mutant forms of 5' ALT /p16<sup>INK4A</sup> or 5' ALT/p15<sup>INK4B</sup> in a cell with the generation of a malignant hyperproliferative state such that there might exist an expectation that expression of 5' ALT /p16<sup>INK4A</sup> or 5' ALT/p15<sup>INK4B</sup> would reverse that phenotype. The post-filing evidence previously submitted, i.e. the Liggett et al. reference, describes *in vitro*

that the gene with a splice site encoding a

splice variant. The reference makes no mention of the

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that the applicant have stated for the record that p16 $\beta$  is 5' ALT-l6. Liggett et al. demonstrates that expression of p16 $\beta$  results in decreased survival of tumors cell lines *in vitro* with mutations in p16 or p16 $\beta$ . While these results provide an indication that p16 $\beta$  expression can affect the rate of growth of a tumor cell with a mutation in p16 or p16 $\beta$  *in vitro*, they provide no guidance for the actual treatment of tumors *in vivo*. Liggett et al. does not teach any routes of *in vivo* vector delivery, levels of p16 $\beta$  expression *in vivo*, vectors other than a plasmid vector encoding p16 $\beta$ , or 5'ALT polypeptides other than p16 $\beta$ . Thus, the results presented by Liggett et al. are not commensurate in scope with the instant claims and further fail to provide a nexus between the disclosed *in vitro* assays and the instant methods of treating tumors *in vivo*. In addition, the post-filing evidence has no bearing on the putative 5' ALT/p15<sup>INK4B</sup> polypeptide. As noted in the previous office action, the specification fails to provide any guidance or evidence that decreased transcription of the 5' ALT/p15<sup>INK4B</sup> polynucleotide is associated with a malignant phenotype in any type of tumor. Furthermore, in view of the complex pattern of mutations that results in the generation of a malignant hyperproliferative cell, see Vogelstein et al., the skilled artisan would not have been able to predict in the absence of specific evidence whether the correction of a single mutation in a malignant cell would result in the reversal of the hyperproliferative phenotype.

The applicant further argues that the amendment to the instant claims which limits the route of delivery to local administration to the site of the cells to be treated overcomes any

contacted with the target cells. Please note however that the polynucleotide recited in the claims

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as amended reads on a polynucleotide comprising SEQ ID NO:1 operatively linked to a polynucleotide comprising exons 2 and 3 of the p16 gene or exon 2 of p15 in the absence of any expression regulatory elements such as a promoter or enhancer. The specification does not provide any guidance for expressing the recited polynucleotides in the absence of expression regulatory elements. Further, as noted in prior office actions, the specification does not provide sufficient guidance for inhibiting the proliferation of tumors *in vivo* in any and all animals using any DNA construct or expression construct. The specification discloses that both viral and non-viral vectors can be used to express the 5' ALT polynucleotide, including adenoviral and retroviral vectors. The specification fails to provide any guidance as to the level of 5' ALT polypeptide expression that correlates with decreased tumor growth in any type of malignant hyperproliferative cell with decreased expression of 5' ALT /p16<sup>INK4A</sup>, 5' ALT/p15<sup>INK4B</sup>, or p16 *in vivo*. As discussed in detail in previous office actions, at the time of filing, *in vivo* gene therapy utilizing the direct administration of recombinant nucleic acids, whether in the form of retroviruses, adenoviruses, or plasmid DNA/liposome complexes, was considered to be highly unpredictable (Verma et al., Marshall et al., and Orkin et al. ). Among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are anti-viral immune responses, particularly against adenoviral proteins, and the identity of the promoter used to drive gene expression. Thus, the art at the time of filing clearly establishes that expectation for

that the specification fails to provide any guidance as to the level of 5' ALT polypeptide expression that correlates with decreased tumor growth in any type of malignant hyperproliferative cell with decreased expression of 5' ALT /p16<sup>INK4A</sup>, 5' ALT/p15<sup>INK4B</sup>, or p16 *in vivo*. As discussed in detail in previous office actions, at the time of filing, *in vivo* gene therapy utilizing the direct administration of recombinant nucleic acids, whether in the form of retroviruses, adenoviruses, or plasmid DNA/liposome complexes, was considered to be highly unpredictable (Verma et al., Marshall et al., and Orkin et al. ). Among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are anti-viral immune responses, particularly against adenoviral proteins, and the identity of the promoter used to drive gene expression. Thus, the art at the time of filing clearly establishes that expectation for

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amendment has overcome the lack of enablement for using any and all routes of polynucleotide delivery, the amendment has not overcome the unpredictability for achieving therapeutic levels of gene expression in the target cells using any polynucleotide which comprises SEQ ID NO:1 operatively linked to a polynucleotide comprising exons 2 and 3 of the p16 gene or exon 2 of p15.

Finally, the applicant is reminded that 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). The office submits that the specification and evidence of record have been analyzed in direct accordance to the factors outlined in *In re Wands*, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, and 5) the presence or absence of working examples, and presented detailed scientific reasons supported by references from the prior art for the finding of lack of enablement for the scope of the instant methods. Thus, due to the art recognized unpredictability of achieving therapeutic levels of gene expression following direct nucleic acid vectors, the lack of guidance provided by the specification for the parameters affecting delivery and expression of therapeutic amounts of 5' ALT /p16<sup>INK4A</sup> or 5' ALT/p15<sup>INK4B</sup> in tumor cells in a mammal as discussed above, the lack of guidance concerning the biological activities of 5' ALT /p16<sup>INK4A</sup> or 5' ALT/p15<sup>INK4B</sup> polypeptides, the lack of working examples, and the breadth of the claims, it would have required

that persons of ordinary skill in the art could not have predicted success in achieving the claimed results without undue experimentation.

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ALT /p16<sup>INK4A</sup> or 5' ALT/p15<sup>INK4B</sup> using any vector encoding 5' ALT /p16<sup>INK4A</sup> or 5' ALT/p15<sup>INK4B</sup> respectively. The applicant is reminded that "Case law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves." *In re Gardner* 166 USPQ 138 (CCPA) 1970.

No Claims are allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne M. ... (b) (7)(C), (b) (7)(D), (b) (7)(F), (b) (7)(G), (b) (7)(H), (b) (7)(I), (b) (7)(J), (b) (7)(K), (b) (7)(L), (b) (7)(M), (b) (7)(N), (b) (7)(O), (b) (7)(P), (b) (7)(Q), (b) (7)(R), (b) (7)(S), (b) (7)(T), (b) (7)(U), (b) (7)(V), (b) (7)(W), (b) (7)(X), (b) (7)(Y), (b) (7)(Z), (b) (7)(AA), (b) (7)(AB), (b) (7)(AC), (b) (7)(AD), (b) (7)(AE), (b) (7)(AF), (b) (7)(AG), (b) (7)(AH), (b) (7)(AI), (b) (7)(AJ), (b) (7)(AK), (b) (7)(AL), (b) (7)(AM), (b) (7)(AN), (b) (7)(AO), (b) (7)(AP), (b) (7)(AQ), (b) (7)(AR), (b) (7)(AS), (b) (7)(AT), (b) (7)(AU), (b) (7)(AV), (b) (7)(AW), (b) (7)(AX), (b) (7)(AY), (b) (7)(AZ), (b) (7)(BA), (b) (7)(BB), (b) (7)(BC), (b) (7)(BD), (b) (7)(BE), (b) (7)(BF), (b) (7)(BG), (b) (7)(BH), (b) (7)(BI), (b) (7)(BJ), (b) (7)(BK), (b) (7)(BL), (b) (7)(BM), (b) (7)(BN), (b) (7)(BO), (b) (7)(BP), (b) (7)(BQ), (b) (7)(BR), (b) (7)(BS), (b) (7)(BT), (b) (7)(BU), (b) (7)(BV), (b) (7)(BW), (b) (7)(BX), (b) (7)(BY), (b) (7)(BZ), (b) (7)(CA), (b) (7)(CB), (b) (7)(CC), (b) (7)(CD), (b) (7)(CE), (b) (7)(CF), (b) (7)(CG), (b) (7)(CH), (b) (7)(CI), (b) (7)(CJ), (b) (7)(CK), (b) (7)(CL), (b) (7)(CM), (b) (7)(CN), (b) (7)(CO), (b) (7)(CP), (b) (7)(CQ), (b) (7)(CR), (b) (7)(CS), (b) (7)(CT), (b) (7)(CU), (b) (7)(CV), (b) (7)(CW), (b) (7)(CX), (b) (7)(CY), (b) (7)(CZ), (b) (7)(DA), (b) (7)(DB), (b) (7)(DC), (b) (7)(DD), (b) (7)(DE), (b) (7)(DF), (b) (7)(DG), (b) (7)(DH), (b) (7)(DI), (b) (7)(DJ), (b) (7)(DK), (b) (7)(DL), (b) (7)(DM), (b) (7)(DN), (b) (7)(DO), (b) (7)(DP), (b) (7)(DQ), (b) (7)(DR), (b) (7)(DS), (b) (7)(DT), (b) (7)(DU), (b) (7)(DV), (b) (7)(DW), (b) (7)(DX), (b) (7)(DY), (b) (7)(DZ), (b) (7)(EA), (b) (7)(EB), (b) (7)(EC), (b) (7)(ED), (b) (7)(EE), (b) (7)(EF), (b) (7)(EG), (b) (7)(EH), (b) (7)(EI), (b) (7)(EJ), (b) (7)(EK), (b) (7)(EL), (b) (7)(EM), (b) (7)(EN), (b) (7)(EO), (b) (7)(EP), (b) (7)(EQ), (b) (7)(ER), (b) (7)(ES), (b) (7)(ET), (b) (7)(EU), (b) (7)(EV), (b) (7)(EW), (b) (7)(EX), (b) (7)(EY), (b) (7)(EZ), (b) (7)(FA), (b) (7)(FB), (b) (7)(FC), (b) (7)(FD), (b) (7)(FE), (b) (7)(FF), (b) (7)(FG), (b) (7)(FH), (b) (7)(FI), (b) (7)(FJ), (b) (7)(FK), (b) (7)(FL), (b) (7)(FM), (b) (7)(FN), (b) (7)(FO), (b) (7)(FP), (b) (7)(FQ), (b) (7)(FR), (b) (7)(FS), (b) (7)(FT), (b) (7)(FU), (b) (7)(FV), (b) (7)(FW), (b) (7)(FX), (b) (7)(FY), (b) (7)(FZ), (b) (7)(GA), (b) (7)(GB), (b) (7)(GC), (b) (7)(GD), (b) (7)(GE), (b) (7)(GF), (b) (7)(GG), (b) (7)(GH), (b) (7)(GI), (b) (7)(GJ), (b) (7)(GK), (b) (7)(GL), (b) (7)(GM), (b) (7)(GN), (b) (7)(GO), (b) (7)(GP), (b) (7)(GQ), (b) (7)(GR), (b) (7)(GS), (b) (7)(GT), (b) (7)(GU), (b) (7)(GV), (b) (7)(GW), (b) (7)(GX), (b) (7)(GY), (b) (7)(GZ), (b) (7)(HA), (b) (7)(HB), (b) (7)(HC), (b) (7)(HD), (b) (7)(HE), (b) (7)(HF), (b) (7)(HG), (b) (7)(HH), (b) (7)(HI), (b) (7)(HJ), (b) (7)(HK), (b) (7)(HL), (b) (7)(HM), (b) (7)(HN), (b) (7)(HO), (b) (7)(HP), (b) (7)(HQ), (b) (7)(HR), (b) (7)(HS), (b) (7)(HT), (b) (7)(HU), (b) (7)(HV), (b) (7)(HW), (b) (7)(HX), (b) (7)(HY), (b) (7)(HZ), (b) (7)(IA), (b) (7)(IB), (b) (7)(IC), (b) (7)(ID), (b) (7)(IE), (b) (7)(IF), (b) (7)(IG), (b) (7)(IH), (b) (7)(II), (b) (7)(IJ), (b) (7)(IK), (b) (7)(IL), (b) (7)(IM), (b) (7)(IN), (b) (7)(IO), (b) (7)(IP), (b) (7)(IQ), (b) (7)(IR), (b) (7)(IS), (b) (7)(IT), (b) (7)(IU), (b) (7)(IV), (b) (7)(IW), (b) (7)(IX), (b) (7)(IY), (b) (7)(IZ), (b) (7)(JA), (b) (7)(JB), (b) (7)(JC), (b) (7)(JD), (b) (7)(JE), (b) (7)(JF), (b) (7)(JG), (b) (7)(JH), (b) (7)(JI), (b) (7)(JJ), (b) (7)(JK), (b) (7)(JL), (b) (7)(JM), (b) (7)(JN), (b) (7)(JO), (b) (7)(JP), (b) (7)(JQ), (b) (7)(JR), (b) (7)(JS), (b) (7)(JT), (b) (7)(JU), (b) (7)(JV), (b) (7)(JW), (b) (7)(JX), (b) (7)(JY), (b) (7)(JZ), (b) (7)(KA), (b) (7)(KB), (b) (7)(KC), (b) (7)(KD), (b) (7)(KE), (b) (7)(KF), (b) (7)(KG), (b) (7)(KH), (b) (7)(KI), (b) (7)(KJ), (b) (7)(KK), (b) (7)(KL), (b) (7)(KM), (b) (7)(KN), (b) (7)(KO), (b) (7)(KP), (b) (7)(KQ), (b) (7)(KR), (b) (7)(KS), (b) (7)(KT), (b) (7)(KU), (b) (7)(KV), (b) (7)(KW), (b) (7)(KX), (b) (7)(KY), (b) (7)(KZ), (b) (7)(LA), (b) (7)(LB), (b) (7)(LC), (b) (7)(LD), (b) (7)(LE), (b) (7)(LF), (b) (7)(LG), (b) (7)(LH), (b) (7)(LI), (b) (7)(LJ), (b) (7)(LK), (b) (7)(LL), (b) (7)(LM), (b) (7)(LN), (b) (7)(LO), (b) (7)(LP), (b) (7)(LQ), (b) (7)(LR), (b) (7)(LS), (b) (7)(LT), (b) (7)(LU), (b) (7)(LV), (b) (7)(LW), (b) (7)(LX), (b) (7)(LY), (b) (7)(LZ), (b) (7)(MA), (b) (7)(MB), (b) (7)(MC), (b) (7)(MD), (b) (7)(ME), (b) (7)(MF), (b) (7)(MG), (b) (7)(MH), (b) (7)(MI), (b) (7)(MJ), (b) (7)(MK), (b) (7)(ML), (b) (7)(MM), (b) (7)(MN), (b) (7)(MO), (b) (7)(MP), (b) (7)(MQ), (b) (7)(MR), (b) (7)(MS), (b) (7)(MT), (b) (7)(MU), (b) (7)(MV), (b) (7)(MW), (b) (7)(MX), (b) (7)(MY), (b) (7)(MZ), (b) (7)(NA), (b) (7)(NB), (b) (7)(NC), (b) (7)(ND), (b) (7)(NE), (b) (7)(NF), (b) (7)(NG), (b) (7)(NH), (b) (7)(NI), (b) (7)(NJ), (b) (7)(NK), (b) (7)(NL), (b) (7)(NM), (b) (7)(NN), (b) (7)(NO), (b) (7)(NP), (b) (7)(NQ), (b) (7)(NR), (b) (7)(NS), (b) (7)(NT), (b) (7)(NU), (b) (7)(NV), (b) (7)(NW), (b) (7)(NX), (b) (7)(NY), (b) (7)(NZ), (b) (7)(OA), (b) (7)(OB), (b) (7)(OC), (b) (7)(OD), (b) (7)(OE), (b) (7)(OF), (b) (7)(OG), (b) (7)(OH), (b) (7)(OI), (b) (7)(OJ), (b) (7)(OK), (b) (7)(OL), (b) (7)(OM), (b) (7)(ON), (b) (7)(OO), (b) (7)(OP), (b) (7)(OQ), (b) (7)(OR), (b) (7)(OS), (b) (7)(OT), (b) (7)(OU), (b) (7)(OV), (b) (7)(OW), (b) (7)(OX), (b) (7)(OY), (b) (7)(OZ), (b) (7)(PA), (b) (7)(PB), (b) (7)(PC), (b) (7)(PD), (b) (7)(PE), (b) (7)(PF), (b) (7)(PG), (b) (7)(PH), (b) (7)(PI), (b) (7)(PJ), (b) (7)(PK), (b) (7)(PL), (b) (7)(PM), (b) (7)(PN), (b) (7)(PO), (b) (7)(PP), (b) (7)(PQ), (b) (7)(PR), (b) (7)(PS), (b) (7)(PT), (b) (7)(PU), (b) (7)(PV), (b) (7)(PW), (b) (7)(PX), (b) (7)(PY), (b) (7)(PZ), (b) (7)(QA), (b) (7)(QB), (b) (7)(QC), (b) (7)(QD), (b) (7)(QE), (b) (7)(QF), (b) (7)(QG), (b) (7)(QH), (b) (7)(QI), (b) (7)(QJ), (b) (7)(QK), (b) (7)(QL), (b) (7)(QM), (b) (7)(QN), (b) (7)(QO), (b) (7)(QP), (b) (7)(QQ), (b) (7)(QR), (b) (7)(QS), (b) (7)(QT), (b) (7)(QU), (b) (7)(QV), (b) (7)(QW), (b) (7)(QX), (b) (7)(QY), (b) (7)(QZ), (b) (7)(RA), (b) (7)(RB), (b) (7)(RC), (b) (7)(RD), (b) (7)(RE), (b) (7)(RF), (b) (7)(RG), (b) (7)(RH), (b) (7)(RI), (b) (7)(RJ), (b) (7)(RK), (b) (7)(RL), (b) (7)(RM), (b) (7)(RN), (b) (7)(RO), (b) (7)(RP), (b) (7)(RQ), (b) (7)(RR), (b) (7)(RS), (b) (7)(RT), (b) (7)(RU), (b) (7)(RV), (b) (7)(RW), (b) (7)(RX), (b) (7)(RY), (b) (7)(RZ), (b) (7)(SA), (b) (7)(SB), (b) (7)(SC), (b) (7)(SD), (b) (7)(SE), (b) (7)(SF), (b) (7)(SG), (b) (7)(SH), (b) (7)(SI), (b) (7)(SJ), (b) (7)(SK), (b) (7)(SL), (b) (7)(SM), (b) (7)(SN), (b) (7)(SO), (b) (7)(SP), (b) (7)(SQ), (b) (7)(SR), (b) (7)(SS), (b) (7)(ST), (b) (7)(SU), (b) (7)(SV), (b) (7)(SW), (b) (7)(SX), (b) (7)(SY), (b) (7)(SZ), (b) (7)(TA), (b) (7)(TB), (b) (7)(TC), (b) (7)(TD), (b) (7)(TE), (b) (7)(TF), (b) (7)(TG), (b) (7)(TH), (b) (7)(TI), (b) (7)(TJ), (b) (7)(TK), (b) (7)(TL), (b) (7)(TM), (b) (7)(TN), (b) (7)(TO), (b) (7)(TP), (b) (7)(TQ), (b) (7)(TR), (b) (7)(TS), (b) (7)(TT), (b) (7)(TU), (b) (7)(TV), (b) (7)(TW), (b) (7)(TX), (b) (7)(TY), (b) (7)(TZ), (b) (7)(UA), (b) (7)(UB), (b) (7)(UC), (b) (7)(UD), (b) (7)(UE), (b) (7)(UF), (b) (7)(UG), (b) (7)(UH), (b) (7)(UI), (b) (7)(UJ), (b) (7)(UK), (b) (7)(UL), (b) (7)(UM), (b) (7)(UN), (b) (7)(UO), (b) (7)(UP), (b) (7)(UQ), (b) (7)(UR), (b) (7)(US), (b) (7)(UT), (b) (7)(UU), (b) (7)(UV), (b) (7)(UW), (b) (7)(UX), (b) (7)(UY), (b) (7)(UZ), (b) (7)(VA), (b) (7)(VB), (b) (7)(VC), (b) (7)(VD), (b) (7)(VE), (b) (7)(VF), (b) (7)(VG), (b) (7)(VH), (b) (7)(VI), (b) (7)(VJ), (b) (7)(VK), (b) (7)(VL), (b) (7)(VM), (b) (7)(VN), (b) (7)(VO), (b) (7)(VP), (b) (7)(VQ), (b) (7)(VR), (b) (7)(VS), (b) (7)(VT), (b) (7)(VU), (b) (7)(VV), (b) (7)(VW), (b) (7)(VX), (b) (7)(VY), (b) (7)(VZ), (b) (7)(WA), (b) (7)(WB), (b) (7)(WC), (b) (7)(WD), (b) (7)(WE), (b) (7)(WF), (b) (7)(WG), (b) (7)(WH), (b) (7)(WI), (b) (7)(WJ), (b) (7)(WK), (b) (7)(WL), (b) (7)(WM), (b) (7)(WN), (b) (7)(WO), (b) (7)(WP), (b) (7)(WQ), (b) (7)(WR), (b) (7)(WS), (b) (7)(WT), (b) (7)(WU), (b) (7)(WV), (b) (7)(WW), (b) (7)(WX), (b) (7)(WY), (b) (7)(WZ), (b) (7)(XA), (b) (7)(XB), (b) (7)(XC), (b) (7)(XD), (b) (7)(XE), (b) (7)(XF), (b) (7)(XG), (b) (7)(XH), (b) (7)(XI), (b) (7)(XJ), (b) (7)(XK), (b) (7)(XL), (b) (7)(XM), (b) (7)(XN), (b) (7)(XO), (b) (7)(XP), (b) (7)(XQ), (b) (7)(XR), (b) (7)(XS), (b) (7)(XT), (b) (7)(XU), (b) (7)(XV), (b) (7)(XW), (b) (7)(XX), (b) (7)(XY), (b) (7)(XZ), (b) (7)(YA), (b) (7)(YB), (b) (7)(YC), (b) (7)(YD), (b) (7)(YE), (b) (7)(YF), (b) (7)(YG), (b) (7)(YH), (b) (7)(YI), (b) (7)(YJ), (b) (7)(YK), (b) (7)(YL), (b) (7)(YM), (b) (7)(YN), (b) (7)(YO), (b) (7)(YP), (b) (7)(YQ), (b) (7)(YR), (b) (7)(YS), (b) (7)(YT), (b) (7)(YU), (b) (7)(YV), (b) (7)(YW), (b) (7)(YX), (b) (7)(YY), (b) (7)(YZ), (b) (7)(ZA), (b) (7)(ZB), (b) (7)(ZC), (b) (7)(ZD), (b) (7)(ZE), (b) (7)(ZF), (b) (7)(ZG), (b) (7)(ZH), (b) (7)(ZI), (b) (7)(ZJ), (b) (7)(ZK), (b) (7)(ZL), (b) (7)(ZM), (b) (7)(ZN), (b) (7)(ZO), (b) (7)(ZP), (b) (7)(ZQ), (b) (7)(ZR), (b) (7)(ZS), (b) (7)(ZT), (b) (7)(ZU), (b) 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